Canada's Drug Agency
L'Agence des médicaments du Canada

CDA-AMC REIMBURSEMENT REVIEW

Patient, Clinician and Industry Input

nivolumab

(non-sponsored review)

Indication: With doxorubicin, vinblastine and dacarbazine (AVD) in previously untreated stage III or IV Hodgkin Lymphoma.

January 17, 2025

This document compiles the input submitted by patient groups and clinician groups for the file under review. The information is used by CDA-AMC in all phases of the review, including the appraisal of evidence and interpretation of the results. The input submitted for each review is also included in the briefing materials that are sent to expert committee members prior to committee meetings. **If your group has submitted input that is not reflected within this document, please contact Formulary-Support@cda-amc.ca.**

Disclaimer: The views expressed in this submission are those of the submitting organization or individual. As such, they are independent of CDA-AMC and do not necessarily represent or reflect the views of CDA-AMC. No endorsement by CDA-AMC is intended or should be inferred.

By filing with CDA-AMC, the submitting organization or individual agrees to the full disclosure of the information. CDA-AMC does not edit the content of the submissions received.

CDA-AMC does use reasonable care to prevent disclosure of personal information in posted material; however, it is ultimately the submitter's responsibility to ensure no identifying personal information or personal health information is included in the submission. The name of the submitting group and all conflicts of interest information from individuals who contributed to the

CADTH

CADTH Reimbursement Review
Patient Input Template

Patient Input Template for CADTH Reimbursement Reviews

Name of Drug: Nivolumab (Opdivo)

Indication: Nivolumab with doxorubicin, vinblastine and dacarbazine (AVD) in previously untreated stage III or IV Hodgkin Lymphoma.

Name of Patient Group: Lymphoma Canada

Author of Submission: Gurjot Basra, Manager of Patient Programs, Research, and Advocacy

1. About Your Patient Group

Lymphoma Canada is a national Canadian registered charity whose mission it is to empower patients and the lymphoma community through education, support, advocacy, and research. Based out of Mississauga (ON), we collaborate with patients, caregivers, healthcare professionals, and other organizations and stakeholders, to promote early detection, find new and better treatments for lymphoma patients, help patients access those treatments, learn about the causes of lymphoma, and work together to find a cure. Resources are provided in both English and French. www.lymphoma.ca

2. Information Gathering

The data presented in this submission was collected from an online anonymous patient survey, created and promoted by Lymphoma Canada (LC) available from December 16 2024 to January 16, 2025. The link was promoted via e-mail to patients registered in the LC national emailing list and made available via social media outlets, including Instagram, and Facebook accounts. The survey had a combination of multiple choice, rating, and open-ended questions. Skipping logic was built into the survey so that respondents were asked questions only relevant to them. Open-ended responses were noted in this report verbatim, to provide a deeper understanding of patient perspectives. 48 responses were collected amongst those who had Hodgkin Lymphoma (HL). Information from this survey was used to identify the main areas of concern for patients with HL, with 2 confirmed responses for experience with Nivolumab, one patient located in Canada and the other from the United States. Of the two patients who received this therapy, both were male, ages ranging from 35-44 years and 65-74 years respectively.

Please see tables 1-6 below for demographic and relevant information of all survey respondents. The majority of patients lived in Canada (87%), between the age of 65 and 74 (33%) or 35 and 44 (25%), female (52%), and were diagnosed 9-10 years ago (25%), less than a year ago (25%), or 5-8 years ago (17%) with most diagnosed with Classical Hodgkin Lymphoma - Nodular Sclerosis, Stage III or IV.

Table 1: Country of respondents from Lymphoma Canada survey

Respondents	CAN	USA	United Kingdom	Total
Patients with Hodgkin Lymphoma	42	3	3	48

Table 2: Age range of respondents from Lymphoma Canada survey

Respondents	Age (years old)						
	18-24	25-34	35-54	45-54	55-64	65-74	Total
Patients with Hodgkin Lymphoma	4	4	12	8	4	16	48

Table 3: Gender of respondents from Lymphoma Canada survey

Respondents	Gender			
	Female	Male	Skipped	Total
Patients with Hodgkin Lymphoma	25	8	15	48

Table 4: Number of years ago respondents were diagnosed with HL

Respondents	Years						
	<1	1-2	3-5	5-8	9-10	Skipped	Total
Patients with Hodgkin Lymphoma	12	6	6	8	12	4	48

Table 5: Type of HL

Subtype of Hodgkin Lymphoma	Number of respondents
Classical Hodgkin Lymphoma	22
Classical HL - Nodular Sclerosis	13

Classical HL - Mixed Cellularity	3
Classical HL - Lymphocyte-rich	0
Classical HL - Lymphocyte-depleted	0
Nodular lymphocyte-predominant B-cell lymphoma (NLPBL)	4
Not sure	6
Total	48

Table 6: Stage of HL at Diagnosis

Subtype of Hodgkin Lymphoma	Number of respondents
Stage I – Localized disease: one group of lymph nodes affected	4
Stage II – Two or more groups of lymph nodes are affected but they are all in the chest or all in the abdomen	10
Stage III – Two or more groups of lymph nodes are affected in both the chest and the abdomen with or without involvement of a nearby organ	12
Stage IV – Widespread disease: lymphoma is in multiple organs or tissues (e.g., bone marrow, liver or lungs) and may also be in the lymph nodes	14
I don't know the stage of my diagnosis	8

3. Disease Experience

At Diagnosis

Through Lymphoma Canada's online survey, patients were asked to rate a list of physical symptoms on a scale of 1 (no impact) to 5 (significant impact) in regards to their quality of life upon diagnosis. The most common reported symptoms rated as a four or five were: Enlarged lymph nodes (52%), fatigue/lack of energy (44%), body aches and pains (33%), Indigestion, abdominal pain or bloating (29%), itching that grows steadily worse over time (29%), and night sweats (24%).

Respondents of the survey were also asked to select from a list of psychosocial impacts they experienced when diagnosed with HL. Of the 48 patients that responded to the survey question, 79% experienced stress/anxiety/worry, 61% were fearful of progression, 47% were fearful of not being able to continue daily activities, and 42% had difficulty sleeping.

When asked to provide additional details about the challenges faced during diagnosis, patients commented on the difficulty of getting a diagnosis in the first place, as well as additional details regarding symptoms experienced and increased anxiety/fears:

- “Biggest challenge was getting a diagnosis and getting access to the health care system for biopsies! It took 6 months to get 3 biopsies and start chemotherapy!”
- “Not very hungry, lost lots of weight , shortness of breath”
- “fear of death; pain; fear of blood test results; fear of doctors appointments”
- “I have trouble falling asleep, often have night sweats”
- “My anxiety and stress from the diagnosis is overbearing and all consuming”

Current Quality of Life

To understand the factors which currently impact patients with Hodgkin Lymphoma, respondents were asked a similar style of questions from the diagnosis section of the survey. On a scale of 1 (no impact) to 5 (significant impact), 72% of patients rated fatigue and lack of energy as a 4 or 5, and 36% of patients rated weight loss and frequent infections as a 4 or 5.

Patients also indicated they recently experienced mental health challenges such as anxiety/worry (86%), fear of progression/relapse (78%), and stress of having cancer (71%).

Daily Activities

Regarding day-to-day activities, patients with Hodgkin lymphoma rated several factors on a scale of 1 (no impact) to 5 (very significant impact) which impacted their daily life. In this regard, the ability to work, school and volunteer (57%), the ability to travel (50%), the ability to exercise (43%), the ability to fulfill family obligations (43%), and the ability to spend time with family and friends (36%) were rated as a 4 or higher. Many patients left comments in this section and a selection of quotes are included below:

- “I have depression, feel extremely fatigued and I overeat. I feel like I am in a rut”
- “I feel significantly slower, and am experiencing a lot of fatigue”
- “Although I have been considered “cured” of my cancer, I can’t help but feel fearful that the cancer will return”
- “I still get mouth sensitivity on a fairly regular basis. I didn't get mouth sores during chemo treatment but I experienced mouth sensitivity in the back of my mouth (both sides) that I still experience to this day. It often happens when I don't eat for a few hours so it's like a sudden shock to my mouth. It isn't painful or anything just uncomfortable as it's similar to eating something very sour and one's mouth

flinches. I also get tired more easily than before having cancer. It may result in me having to rest for a bit and lay down."

- "Fatigue is the worst for me, I had to take significant time off of work"
- "I am approaching the five year mark since I was diagnosed as cancer-free following chemotherapy treatment, and so far so good. Other than my Hemoglobin level being a tad low (123), I am feeling fine, and in a sense lucky to have conquered this dreaded disease. My quality of life has returned to what it once was, prior to being diagnosed with cancer in June 2020."

Summary

- For many patients, to live with HL means living with fatigue, anxiety, and stress, and a range of physical symptoms (such as bodily aches and pains, abdominal issues, itching, etc.), all of which have a significant impact on a person's quality of life.

4. Experiences With Currently Available Treatments

Patients who completed the Lymphoma Canada survey were asked how many lines of treatment they received to treat their Hodgkin lymphoma. The majority of patients indicated they received either 1 (38%) or 2+ (54%) lines of treatment, see Table 7.

Table 7: Number of lines of therapy survey respondents received

Respondents	Have not yet received therapy	1	2	3+	Skipped	Total
Patients with Hodgkin Lymphoma	1	5	2	5	35	48

In the front-line setting, 8 patients received ABVD - doxorubicin, bleomycin, vinblastine and dacarbazine, 3 patients received Brentuximab + AVD, 1 received AVD. In second line +, treatments received included brentuximab, salvage chemotherapy, High-Dose Chemotherapy with Stem Cell Transplantation (Autologous or Allogeneic), Pembrolizumab, or involvement in clinical trials.

These patients were asked: "How satisfied were you with the number of treatment options available to you for your lymphoma?" 75% of patients indicated they were very satisfied or satisfied with their frontline treatment options. While 30% of survey respondents gave the same rating in second-line treatment, and 10% with their third-line treatment options.

When asked which side effects were the most difficult to tolerate many patients indicated fatigue, hair loss, bone/muscle pain, nausea, loss of appetite/weight loss, constipation, bodily aches and pain, mouth sores, and diarrhea. Some patient remarks to this question:

- “Diarrhea was worst. Sleepless nights also very bad; lethargic but lack of rest/sleep”
- “Lack of energy, unable to work”
- “The extreme fatigue and hair loss were very difficult to tolerate. With each chemo treatment, I would get more and more tired. I also experienced sore arms from the IV. It was often very difficult for the nurses to find a good vein for the IV which made it very stressful. Sometimes it would take 5-10 attempts to hook up the IV (failed attempts)”
- “Nausea, vomiting and anxiety”

12 patients provided information about their ability to access their HL treatment. 6 patients found it not difficult at all or not very difficult to access treatment, while 4 patients had some difficulty and 2 had a lot of difficulty. If patients were not able to access treatment, the main reasons were because the treatment was not available/they could not access the treatment at their local cancer center (45%), or because they lived in a community without a cancer center (27%).

The most common financial implications reported for treatment for HL were absence from work (67%), supplementary drug costs for side effects (50%), travelling costs (50%), drug costs (50%), and medical supplies cost (42%).

Here are some comments from patients in terms of difficulties regarding access to treatment in Canada:

- “I had to travel significantly out of city for treatment”
- “Funding for Pembrolizumab. I had previously had Pembrolizumab for 2 years and wasn’t allowed anymore but after appeal was allowed further treatment.”
- “Brentuximab, bendamustine and pembro were denied by Ontario government. My private benefits paid after I paid the 3500$ deductible”
- “You hit the end of the road beyond 3rd line and are only given an allo transplant option - which besides not being very effective is debilitating with high mortality risks.”
- “Waiting at the hospital for up to 6 hours on every scheduled chemo day. Exhausting.”

Summary of the Current Available Therapies

- Side effects of treatment and their impacts on the patient's quality of life remain a significant issue for survey respondents.

5. Improved Outcomes

HL patients which completed the Lymphoma Canada survey were asked how important it was for a new drug to control/treat their HL. HL patients indicated factors such as longer disease remission (92%), longer survival (92%), control disease symptoms (92%), improved quality of life to perform daily activities (83%), and normalize blood counts (67%), were very important to them.

9 out of these 12 patients (75%) indicated they would be willing to tolerate side effects to access new treatment options if side effects were not very severe and short term. 9 patients (75%) indicated choice is important to them (scored a 7 or higher out of 10) in deciding to take a drug based on known side effects and expected outcomes of treatment. When participants were asked if there is currently a need for more therapy options for patients with Hodgkin lymphoma, 9 patients (75%) answered "yes".

Comments in regards to patient expectations for new therapies to manage lymphoma included:

- "New treatment with fewer side effects are needed"
- "Highly targeted therapies instead of poisoning and resuscitating patients until death"
- "Keep researching. There must be better therapies."

Summary of Improved Outcomes

- HL patients identified factors important for novel treatments, which included longer life span, longer remission, better quality of life and fewer side effects.
- A majority of patients believe it is very important to have choice in their treatment decision and a variety of treatment options to choose from.

6. Experience With Drug Under Review

From survey responses, 2 patients, both male, indicated they were treated with Nivolumab +AVD. One patient is from Canada, the other is from the United States, ages between 35-44 years and the other 65-74 years respectively. One patient is Stage III, and the other has Stage IV classical Hodgkin Lymphoma.

One patient accessed this therapy as part of a clinical trial while the other through private insurance. In terms of the stage of their cancer journey, 1 patient has been in remission for 1-2 years, while the other has relapsed.

The main side effects reported included decreased appetite (1 patient), nausea/vomiting (1 patient), headache (1 patient), and fatigue (both patients). Both patients indicated that fatigue was the most challenging symptom. Psychological impacts included fear of progression/relapse (2), anxiety/worry (2). difficulty sleeping (1), loss of sexual desire (1), problems concentrating (1).

In terms of overall experience with this therapy, both patients rated it as good, and both said they would recommend it to other patients with advanced cHL.

Comment shared by both of these patients:

- “very tolerable.”
- “One of the very few treatments which allowed me to have some semblance of normalcy in my life.”

Summary of Drug under Review

- The patients who had undergone therapy with Nivolumab experienced fewer side effects, primarily fatigue.
- Both patients who received this therapy would recommend the therapy to other advanced cHL patients, despite one patient having relapsed.

7. Companion Diagnostic Test

N/A

8. Anything Else?

Lymphoma Canada advocates for lymphoma patients and their caregivers to have access to novel lymphoma therapies. An increased number of available treatment options gives patients more choice to decide the therapy that aligns with their personal goals in collaboration with their medical care team. Currently, there is an unmet need in terms of treatment options for patients with advanced classical Hodgkin lymphoma (cHL).

Nivolumab + AVD provides a viable option for patients while aligning with patient preferences in terms of longer progression free survival with fewer associated side effects.

Appendix: Patient Group Conflict of Interest Declaration

To maintain the objectivity and credibility of the CADTH reimbursement review process, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This Patient Group Conflict of Interest Declaration is required for participation. Declarations made do not negate or preclude the use of the patient group input. CADTH may contact your group with further questions, as needed.

1. Did you receive help from outside your patient group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your patient group to collect or analyze data used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past 2 years AND who may have direct or indirect interest in the drug under review.

Table 1: Financial Disclosures

Check Appropriate Dollar Range With an X. Add additional rows if necessary.

Company	$0 to 5,000	$5,001 to 10,000	$10,001 to 50,000	In Excess of $50,000
Pfizer				X
Gilead				X
Roche			X	
Incyte			X	
BMS				X

I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this patient group with a company, organization, or entity that may place this patient group in a real, potential, or perceived conflict of interest situation.

Name: Gurjot Basra
Position: Manager of Patient Programs, Research, and Advocacy -
Patient Group: Lymphoma Canada
Date: January 17, 2024

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: **PX0376-000**
Generic Drug Name (Brand Name): **nivolumab (opdivo)**
Indication: Nivolumab with doxorubicin, vinblastine and dacarbazine (AVD) in previously untreated stage III or IV Hodgkin Lymphoma.
Name of Clinician Group: Lymphoma Canada Scientific Advisory Board
Author of Submission: Dr. Kerry Savage, Dr. Pamela Skrabek, Dr. Graeme Fraser

1. About Your Clinician Group

Please describe the purpose of your organization. Include a link to your website (if applicable).

Lymphoma Canada, a national non-for-profit organization for Canadian lymphoma and CLL patients, coordinated the group clinician response. For more information about Lymphoma Canada, please visit www.lymphoma.ca.

The following clinicians, leading experts in lymphoma across Canada, have provided feedback on this therapeutic for the submitted indication: Kerry Savage, Dr. Pamela Skrabek, Dr. Graeme Fraser

2. Information Gathering

Please describe how you gathered the information included in the submission. From SWOG1826 NEJM publication and Phase 2 study JCO 2025.

3. Current Treatments and Treatment Goals

The goal of treatment with Hodgkin's lymphoma is cure. Given the often young population at risk, future toxicity risks are also considered. The best time to cure is with upfront treatment especially given the increased morbidity, mortality and impact on QOL that can occur with treatment for relapsed/refractory disease. BV-AVD emerged as the standard treatment option in Canada after the initial publication of the Echelon 1 study (Connors NEJM 2017). Unfortunately, in Canada it was restricted to stage 4 patients only as the subgroup analysis suggested no difference in stage patients for the primary endpoint, modified PFS. With longer f/u a PFS benefit was demonstrated in stage 3 (Straus Lancet Heme 2020) and in the ITT population an OS benefit was demonstrated with 6 y f/u data (Ansell NEJM 2022). With the latter data, the BC LYTG submitted a request to add stage 3 to the approved indication which was endorsed. Simultaneously, the pediatric regimen BV+AVPEC was also approved in children and adolescents aged 2 years or older in those with stage 2B with bulky or stage 3B, 4A/B. https://www.cda-amc.ca/sites/default/files/2024-09/ph0052_draft_report.pdf Unfortunately, high risk stage 2 is not included in the current approval for AVD-BV thus this group would receive ABVD as per RATHL study with PET2 negative cases having omission of bleomycin. PET2 positive either are dose escalated to BEACOPP, switched to second-line salvage (with progression) or continue ABVD. In some centres, BEACOPP is used

first with PET adapted approach to guide number of treatment cycles (HD18). Although AVD-BV has changed the treatment landscape, it is associated with often clinically significant peripheral neuropathy. It also is associated with a higher risk of neutropenia and febrile neutropenia, mandating use of grastofil when used. In patients over the age of 60 y, there was no benefit observed with AVD-BV over ABVD and there is increased toxicity, even death and thus most do not used this combination in this age group. BEACOPP is associated with increased acute and chronic toxicities and is only used in those < 60 years. Importantly, it can cause sterility/infertility mandating preservation in the AYA population. Given that second-line treatment involves auto-SCT it is imperative to increase the cure rate in first line but also consider long term effects given the young population at risk. Further, for patients over the age of 60 y who relapse, auto-SCT may not be an option further highlighting the need for better therapies in this age group.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

Although ABVD cures approximately 80% those with IPS 3 or more have a cure rate of 70% or less.
Further those that are PET2 positive continue ABVD or switch to BEACOPP both of which can increase lung toxicity as well as added additional acute/chronic toxicities with the latter .
Further these regimens are often given with RT if there is a positive PET scan at the end of treatment.
Increasing the cure rate in first -line, reduces the need for second line therapy which commonly includes consolidative auto-SCT. As described older patients are not candidates and with inferior outcomes with ABVD c/w younger patients (Cheng Blood Advances) and not clear benefit of AVD-BV better treatments are needed.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

The SWOG1826 study compared standard AVD-BV to AVD-nivolumab in newly diagnosed patients with stage 3 and 4 classical Hodgkin lymphoma. Previous studies highlight the universal expression of PDL cHL and unprecedented response rates compared with other cancers. Further studies demonstrate the synergy between PD1 inhibitors like nivolumab and cytotoxic agents, setting the stage for combination therapy.

SWOG1826 was reported early as a plenary session at the ASCO 2023 meeting as recommended by the DSMC. With median f/u of 12. 1m a PFS benefit was observed in AVD-nivo vs AVD-BV (1 year 94% vs 86%, p=0.0005). At ASH 2023, the subgroup of patients > 60 years was presented – there was a striking PFS benefit c/w AVD-BV (1 y PFS 93% (AVD-nivo) vs 64%(AVD-BV), p=0.022) and a trend to a reduce risk of death with AVD-Nivo (1 y OS 95% vs 83% p=0.09). The subsequent publication in the NEJM demonstrated at a median f/u of 2.1 y a 2 y PFS of 92% with AVD-nivo vs 83% with AVD-BV (2 y in 60 y + 88% vs 65%). A benefit of AVD-nivo was observed in low risk (IPS 0-3 HR .46 (0.22-0.92)) or high risk (IPS 4-7 (0-.30-0.74). Importantly, RT use was < 1% in both arms and thus improving upfront treatment may also reduce the need for RT and potential for long term complications. Toxicity of AVD-nivo was low, as evidenced by better tolerance in the older age group, especially peripheral neuropathy (29% vs 56%) and

despite the fact that grastofil use was not mandated, febrile neutropenia risk was lso low (6% AVD-nivo vs 7% AVD-BV). Presumed irAEs were low with only hypothyroidism (7%) and hyperthyroidism (3%) occurring at an increased frequency. There were no deaths on treatment.

Would the drug under review be reserved for patients who are intolerant to other treatments or in whom other treatments are contraindicated? No

Is the drug under review expected to cause a shift in the current treatment paradigm? Yes it would shift front-line treatment. PD1 inhibitor therapy should still be available in relapsed patients so this would not be impacted.

Please indicate whether or not it would be appropriate to recommend that patients try other treatments before initiating treatment with drug under review. Please provide a rationale for your perspective. Not applicable – it is not standard practice nor evidenced based to switch from one treatment to another.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

The population best suited for AVD-nivolumab is all patients as per trial eligibility. It should be noted that the recent update of the NCCN guidelines not only includes AVD-nivo as a preferred regimen for stage 3 and 4 cHL but also includes it for unfavorable stage 1 and II (ie with bulky or B symptoms). Many centres include high risk stage 2 in advanced stage protocols as evidenced by inclusion of stage 2B with bulk in the pediatric study which lead to CADTH approval BV-AVPEC in the AYA pediatric group. Although this review is focussed on stage 3/4 patients as per SWOG1826 eligibility, strong consideration should be given to expanding this approval to other advanced stage definitions especially since the prognosis is similar or even worse (in the case of BV-AVPEC study the greatest benefit was seen in bulky stage 2B).

Which patients are most likely to respond to treatment with drug under review? All advanced stage classical Hodgkin lymphoma

Which patients are most in need of an intervention? Advanced stage

Would this differ based on any disease characteristics (e.g., presence or absence of certain symptoms, stage of disease)? Overall those with a higher IPS score have a worse outcome but as outlined, those with low IPS and high IPS both had a statistically significant benefit with AVD-nivolumab over AVD-BV

How would patients best suited for treatment with drug under review be identified (e.g., clinician examination/judgement, laboratory tests (specify), diagnostic tools (specify)) Advanced stage patients with cHL

Are there any issues related to diagnosis? None

Is a companion diagnostic test required? No

Is it likely that misdiagnosis occurs in clinical practice (e.g., underdiagnosis)? No

Is it possible to identify those patients who are most likely to exhibit a response to treatment with drug under review? N/A

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

There is standard response assessment using PET scan +/- CT scan in Hodgkin lymphoma – mid treatment and EOT. Hodgkin lymphoma is curative thus goal is complete remission.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

This rarely happens with upfront treatment but if there were a serious AE and in particularly irAE, nivolumab would be discontinued and appropriate treatment with steroids would be given.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

This regimen can be given anywhere – academic or community based setting. Physicians are now very familiar with management of irAEs using single agent PD1 inhibitor therapy and otherwise toxicity monitoring is similar to ABVD.

6. Additional Information

This study represents the most important advancement in Hodgkin lymphoma to date. The magnitude of benefit is clinically meaningful. The benefit in older patients is unprecedented and with the trend seen in reducing the risk of death in older patients, there is an urgent need to move through the approval process quickly. This is not anticipated to have a significant financial impact as these patients would largely have been receiving AVD-BV, especially with stage 3 now approved by CADTH. The last consideration should be for a broader advanced stage inclusion to improve cure rates across all advanced stage definitions. This is particularly relevant in AYA patients as they are more likely to present with high risk stage 2 and use of AVD-Nivo can increase cure rate and reduce the need for RT.

List of References:

1. Rutherford, S.C. *et al.* (2023) 'Nivolumab-AVD is better tolerated and improves progression-free survival compared to BV-AVD in older patients (aged ≥60 years) with advanced stage hodgkin lymphoma enrolled on SWOG S1826', *Blood*, 142(Supplement 1), pp. 181–181. doi:10.1182/blood-2023-180114.
2. Herrera, A.F. *et al.* (2024) 'Nivolumab+AVD in Advanced-Stage Classic Hodgkin's Lymphoma', *New England Journal of Medicine,* 391:1379-89. doi: 10.1056/NEJMoa2405888
3. Connors, J.M. *et al.* (2018) 'Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma', *New England Journal of Medicine*, 378(9), pp. 878–878. doi:10.1056/nejmx180007.
4. Straus, D.J. *et al.* (2020) 'Brentuximab vedotin with chemotherapy for stage III/IV classical hodgkin lymphoma: 3-year update of the ECHELON-1 study', *Blood*, 135(10), pp. 735–742. doi:10.1182/blood.2019003127.
5. Ansell, S.M. *et al.* (2022) ' Overall Survival with Brentuximab Vedotin in Stage III or IV Hodgkin' s Lymphoma', *New England Journal of Medicine, 387:310-20.* doi*:* 10.1056/NEJMoa2206125
6. Cheng, P.T. *et al.* (2022) 'The outcome of older adults with classic hodgkin lymphoma in British Columbia', *Blood Advances*, 6(22), pp. 5924–5932. doi:10.1182/bloodadvances.2022008258.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   No

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Kerry Savage
Position: Medical Oncologist
Date: 12-01-2025

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

Company	Check appropriate dollar range*			
	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000
Seagen	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Pamela Skrabek
Position: Associate Professor, Max Rady College of Medicine, Department of Internal Medicine
Section of Hematology and Medical Oncology, Cancer Care Manitoba

Date: 12-01-2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
Hoffmann-La Roche Ltd.	X			

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 3

Name: Dr. Graeme Fraser
Position: Hematologist, Juravinski Cancer Centre - Director, Malignant Hematology Fellowship Program - Associate Professor, Department of Oncology, McMaster University
Date: 12-01-2025

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 3: Conflict of Interest Declaration for Clinician 3

	Check appropriate dollar range*			
Company	**$0 to $5,000**	**$5,001 to $10,000**	**$10,001 to $50,000**	**In excess of $50,000**
N/A - none				

* Place an X in the appropriate dollar range cells for each company.

CADTH

CADTH Reimbursement Review

Clinician Group Input

CADTH Project Number: PX0376-000
Generic Drug Name (Brand Name): Nivolumab
Indication: Nivolumab with doxorubicin, vinblastine, and dacarbazine (AVD) in previously untreated stage III or IV Hodgkin Lymphoma.
Name of Clinician Group: Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee
Author of Submission: Dr. Tom Kouroukis and members of the Hematology Cancer Drug Advisory Committee

1. About Your Clinician Group

OH-CCO's Cancer Drug Advisory Committees provide timely evidence-based clinical and health system guidance on drug-related issues in support of CCO's mandate, including the Provincial Drug Reimbursement Programs (PDRP) and the Systemic Treatment Program.

2. Information Gathering

Information was gathered via email.

3. Current Treatments and Treatment Goals

For first-line: Brentuximab vedotin (BV)-AVD is the standard of care but only for Stage IV HL patients.

For stage III and IV HL patients, ABVD or BEACOPP depending on their risk and in some cases depending on the results of a PET-directed therapy.

Treatment goals are to achieve cure or delay disease progression or relapse.

4. Treatment Gaps (unmet needs)

4.1. Considering the treatment goals in Section 3, please describe goals (needs) that are not being met by currently available treatments.

The goal is to improve outcomes with first-line therapy so second line therapy is not needed. Nivolumab-AVD has a better progression-free survival than BV-AVD. Brentuximab vedotin is also often associated with significant neuropathy and neutropenia. Nivolumab-AVD would be applicable to older patients and in patients with stage III disease.

5. Place in Therapy

5.1. How would the drug under review fit into the current treatment paradigm?

Nivolumab-AVD will become the standard of care for first line stage III and IV disease.

5.2. Which patients would be best suited for treatment with the drug under review? Which patients would be least suitable for treatment with the drug under review?

As per study, patients with stage III/IV disease.

5.3 What outcomes are used to determine whether a patient is responding to treatment in clinical practice? How often should treatment response be assessed?

Typical lymphoma response measures including PET scan.

5.4 What factors should be considered when deciding to discontinue treatment with the drug under review?

Significant toxicities, or progression.

5.5 What settings are appropriate for treatment with [drug under review]? Is a specialist required to diagnose, treat, and monitor patients who might receive [drug under review]?

Outpatient setting with malignant hematologists.

6. Additional Information

Brentuximab vedotin should still be available as a downstream option for relapsed patients. Patients should also be considered for downstream immunotherapy provided there has not been any disease progression.

Nivolumab cost may be less expensive than brentuximab vedotin per cycle, and with less toxicity.

7. Conflict of Interest Declarations

To maintain the objectivity and credibility of the CADTH drug review programs, all participants in the drug review processes must disclose any real, potential, or perceived conflicts of interest. This conflict of interest declaration is required for participation. Declarations made do not negate or preclude the use of the clinician group input. CADTH may contact your group with further questions, as needed. Please see the *Procedures for CADTH Drug Reimbursement Reviews* (section 6.3) for further details.

1. Did you receive help from outside your clinician group to complete this submission? If yes, please detail the help and who provided it.

   OH-CCO provided secretariat function to the group.

2. Did you receive help from outside your clinician group to collect or analyze any information used in this submission? If yes, please detail the help and who provided it.

   No.

3. List any companies or organizations that have provided your group with financial payment over the past two years AND who may have direct or indirect interest in the drug under review. **Please note that this is required for each clinician who contributed to the input — please add more tables as needed (copy and paste). It is preferred for all declarations to be included in a single document.**

Declaration for Clinician 1

Name: Dr. Tom Kouroukis
Position: Lead, Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee
Date: 28-Nov-2024

☒ **I hereby certify** that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 1: Conflict of Interest Declaration for Clinician 1

	Check appropriate dollar range*			
Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000

* Place an X in the appropriate dollar range cells for each company.

Declaration for Clinician 2

Name: Dr. Jordan Herst
Position: Member, Ontario Health (Cancer Care Ontario) Hematology Cancer Drug Advisory Committee
Date: December 23, 2024

☒ I hereby certify that I have the authority to disclose all relevant information with respect to any matter involving this clinician or clinician group with a company, organization, or entity that may place this clinician or clinician group in a real, potential, or perceived conflict of interest situation.

Table 2: Conflict of Interest Declaration for Clinician 2

	Check appropriate dollar range*			
Company	$0 to $5,000	$5,001 to $10,000	$10,001 to $50,000	In excess of $50,000

* Place an X in the appropriate dollar range cells for each company.

CADTH

CADTH Non-Sponsored Reimbursement Review

Industry Input

CADTH Project Number: PX0376-000
Generic Drug Name: nivolumab
Indication: With doxorubicin, vinblastine and dacarbazine (AVD) in previously untreated stage III or IV Hodgkin Lymphoma.
Name of Organization: BMS
Author of Submission: [redacted]

1. Does the proposed project scope accurately reflect the treatment landscape?

Yes.

2. Are you aware of relevant published studies that you would like considered in the clinical review?

Herrera AF, LeBlanc M, Castellino SM, Li H, Rutherford SC, Evens AM, Davison K, Punnett A, Parsons SK, Ahmed S, Casulo C, Bartlett NL, Tuscano JM, Mei MG, Hess BT, Jacobs R, Saeed H, Torka P, Hu B, Moskowitz C, Kaur S, Goyal G, Forlenza C, Doan A, Lamble A, Kumar P, Chowdhury S, Brinker B, Sharma N, Singh A, Blum KA, Perry AM, Kovach A, Hodgson D, Constine LS, Shields LK, Prica A, Dillon H, Little RF, Shipp MA, Crump M, Kahl B, Leonard JP, Smith SM, Song JY, Kelly KM, Friedberg JW. Nivolumab+AVD in Advanced-Stage Classic Hodgkin's Lymphoma. N Engl J Med. 2024 Oct 17;391(15):1379-1389. doi: 10.1056/NEJMoa2405888. PMID: 39413375; PMCID: PMC11488644.

3. Do you have additional comments that you feel are pertinent to this review?

Increased efficacy and safety with nivolumab: As described in the reference from the New England Journal of Medicine (Herrera, 2024), the treatment with N+AVD resulted in longer progression-free survival than the standard treatment with brentuximab vedotin (BV+AVD) in adolescents and adults with advanced-stage classic Hodgkin lymphoma (stage III or IV) and had a better side-effect profile.

Significant savings opportunity: In addition to the evidence of efficacy and safety published by Herrera et al., the cost of treatment with N+AVD is significantly lower than the cost of the standard treatment currently administered to Canadian patients (BV+AVD). Moreover, prophylaxis with G-CSF is currently added in common practice to patients who receive the current standard of care.

Clinicians feedback: Several clinicians across Canada have contacted BMS to support the conclusion of this publication, indicating that N+AVD has demonstrated clinically significant results in newly diagnosed Hodgkin lymphoma patients.